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(54) Antiviral compounds.

(57) There are provided compounds having the general formulae

$$R-(CH_2)_n-S-R^1; \quad R-(CH_2)_n-\overset{\underset{\|}{O}}{S}-R^1; \quad \text{or} \quad R-(CH_2)_n-\overset{\underset{\|}{O}}{\underset{\overset{\|}{O}}{S}}-R^1$$

I II III

wherein R is an optionally substituted non-fused azole moiety;
n is 5, 6, 7 or 8; and
R^1 is an optionally substituted, fused or non-fused azole moiety.

These compounds have been demonstrated as having antipicornavirus activity.

Also described are intermediate compounds and relevant synthetic processes.

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Description

ANTIVIRAL COMPOUNDS

Field of the Invention

The present invention relates to novel heteroaryl thio, sulfoxy or sulfonyl alkyl azoles. The invention further relates to processes for the preparation of said compounds and to their utility as antiviral agents.

BACKGROUND OF THE INVENTION

The activity of the class of arildone type compounds as antirhinovirus agents has been well documented and disclosed, for example in U.S. Patent 4,171,365 and European Patent Applications 0 111 345 and 0 137 242, respectively.

SUMMARY OF THE INVENTION

In accordance with the present invention there are provided compounds having the general formulae:

$$\underset{\text{I}}{R-(CH_2)_n-S-R^1};\quad \underset{\text{II}}{R-(CH_2)_n-\overset{\displaystyle O}{\overset{\|}{S}}-R^1};\quad \text{or}\quad \underset{\text{III}}{R-(CH_2)_n-\underset{\underset{\displaystyle O}{\|}}{\overset{\overset{\displaystyle O}{\|}}{S}}-R^1}$$

wherein R is preferably selected from the group comprising 3-methylisoxazol-5-yl; 3,5-dimethylpyrazol-1-yl; 4-methylthiazol-2-yl; 4-methylisothiazol-5-yl; or 5-isothiazolyl;
n is 6 or 7; and
R^1 is preferably selected from the group comprising 1-methyltatrazol-5-yl; 5-methyl-1,3,4- thiadiazol-2-yl; 2-benzoxazolyl; 1-methylimidazol-2-yl; 2-benzimidazoyl; 5-chlorobenzimidazol-2-yl; or 2-benzothiazolyl.

Advantageously, physiologically acceptable compounds of formulae I, II, III possess pharmacological properties exhibiting activity, in particular, against rhinoviruses, and coxsackl virus type B-1.

Thus the compounds of the present invention may be utilized as active compounds in medicaments, being formulated with one or more pharmaceutically acceptable carriers.

Broadly stated, the invention comprises compounds having the general formulae :

$$\underset{\text{I}}{R-(CH_2)_n-S-R^1};\qquad \underset{\text{II}}{R-(CH_2)_n-\overset{\displaystyle O}{\overset{\|}{S}}-R^1};\qquad \text{or}\qquad \underset{\text{III}}{R-(CH_2)_n-\underset{\underset{\displaystyle O}{\|}}{\overset{\overset{\displaystyle O}{\|}}{S}}-R^1}$$

wherein R is a non-fused azole moiety;
n is 5, 6, 7 or 8; and
R^1 is a substituted, fused or non-fused azole moiety.

R may suitably be an optionally substituted isoxazolyl, thiazolyl, pyrazolyl or isothiazolyl group, optional substituent(s) suitably being C_{1-4} alkyl group(s), especially methyl. 0,1, or 2 substituents are preferred.

R^1 may suitably be an optionally substituted tetrazolyl, thiadiazolyl, benzoxazolyl, imidazolyl, benzimidoxazolyl or benzothiazolyl group, optional substituents preferably being selected from C_{1-4} alkyl groups, preferably methyl, and halogen atoms, preferably chlorine. 0 or 1 substituent is preferred.

DESCRIPTION OF THE PREFERRED EMBODIMENT

Compounds of formula I were preferably prepared by treating an w-haloalkyl-substituted azole of formula IV
$R-(CH_2)_n-Br$ IV
with a fused or non-fused mercapto azole in a polar aprotic solvent, for example acetone in the presence of a base, for example, potassium carbonate, at an elevated temperature, preferably under reflux.

Compounds of the formulae II and III are suitably prepared by oxidising compounds of formula I with either

metachloroperbenzoic acid or potassium permanganate in suitable solvents.

The w-haloalkyl substituted azoles of formula IV may suitably be prepared according to th conventional procedure of reacting the lithium or sodium salt of the appropriate azole with a dibromo alkane.

The products obtained by each procedure may be purified by recrystallizati n fr m a suitabl solvent or by eluti n from a silica gel c lumn using an appropriate solvent system.

All the products of the invention described hereafter where characterized by their respective nmr, IR spectra and elemental analysis. The relative purity of the compounds was established using HPLC.

More specifically, the w-haloalkyl substituted azoles having the general formula IV may be prepared by reacting a lithium or sodium salt of an azole selected from the group comprising 3,5-dimethylisoxazole; 4-methylthiazole; 4-methylisothiazole; 3,5-dimethylpyrazole or isothiazole with 1,6-dibromohexane in a suitable solvent. The reaction was carried out at a low temperature, for example -50°C to -80°C, preferably about -70°C for 3 - 5 h. The yields varied from 40% to 70%.

The optionally substituted fused, or non-fused, mercapto azoles utilized in the synthesis were selected from the group comprising 5-mercapto-1-methyltetrazole; 2-mercapto-5-methyl-1,3,4-thiadiazole; 2-mercaptobenzoxazole; 2-mercapto-1-methylimidazole; 2-mercaptobenzimidazole; 5-chloro-2-mercapto-benzimidazole; or 2-mercaptobenzothiazole.

The related sulphoxy derivatives of formula I, ie. the compounds of formula II, were prepared by reacting an equimolar amount of the heteroarylthioalkyl azole with metachloroperbenzoic acid (MCPBA) in dichloromethane at room temperature for 0.5 to 2 hours.

Similarly, the related sulphonyl derivatives of formula I, ie., the compounds of formula III, were prepared by reacting a 1:2 ratio of the heteroarylthio alkyl azole with MCPBA, in dichloromethane at room temperature for 0.5 to 2 hours. Alternatively, the heteroarythioalkyl azole may be reacted with potassium permangenate in acetic acid.

The preparation of compounds of formula II is also described in our co-pending co-filed European application entitled "Antiviral Compounds" to which reference should be made for more specific information if required.

Further aspects of the invention are constituted by the process for the prepatation of compounds of the general Formula I, compounds of the general Formula II and their preparation; and by a pharmaceutical composition containing a compound of general formula I.

The selected compounds of this invention were tested for anti-rhinoviral activity and other potential pharmacological activity in accordance with known techniques.

More particularly, 2-[7-(benzoxazol-2-yl)thioheptyl]-4-methylthiazole; 5-(7-(1-methylimidazol-2-yl)thioheptyl]-3-methylisoxazole; 5-[7-(1-methylimidazol-2-yl)sulfoxyheptyl]-3-methylisoxazole; 1-[6-(benzoxazol-2-yl)thiohexyl]-3,5-dimethylpyrazole; 5-[7-(benzimidazol-2-yl)thioheptyl]-3-methylisoxazole; 5-[7-(benzimidazol-2-yl]sulfoxyheptyl]-3-methylisoxazole; 5-[7-(benzothiazol-2-yl)thioheptyl]-3-methylisoxazole; and 2-[6-(5-chlorobenzimidazol-2-yl)thiohexyl]-4-methylthiazole demonstrated remarkable activity against HRV-1A and HRV-39 in vitro.

More particularly, 5-[7-(benzimidazol-2-yl)thioheptyl]-3-methylisoxazole and 2-[6-(5-chlorobenzimidazol-2-yl)thiohexyl]-4-methylthiazole were tasted against 20 zerotypes of rhinoviruses (namely, HRV's 1A, 1B, 2, 4, 15, 17, 23, 29, 30, 31, 32, 36, 39, 44, 49, 53, 56, 63, 86, and 88).

These compounds exhibited MIC-50's which varied from 1 µg/ml to 25 µg/ml.

Compound 2-[6-(5-chlorobenzimidazol-2-yl)thiohexyl]-4-methylthiazole exhibited very strong inhibitory activity against coxsacki virus type B1.

Example 1

5-[7-(1-methyltetrazol-5-yl)thioheptyl]-3-methyl isoxazole. (1)
R = 3-methylisoxazol-5-yl
n = 7
R^1 = 1-methyltetrazol-5-yl.

7-(3-methylisoxazole-5-yl)heptylbromide (520 mg, 0.002 mol) was added to a mixture of 1-methyltetrazole thiol (232 mg, 0.002 mol) and potassium carbonate (276 mg, 0.002 mol) in anhydrous acetone (20 ml) while stirring. The mixture was heated under reflux for 3 hours. After cooling, the mixture was filtered and the filtrate was concentrated under reduced pressure. The residual oil as dissolved in dichloromethane (50 ml), washed with water (50 ml x 2), with 5% aqueous solution of potassium hydroxide (10 ml) and again with water (50 ml x 2). The organic layer was dried over sodium sulfate. Removal of the solvent gave a yellow oil (600 mg) which was purified by elution from a silica gel column using methanol-dichloromethane (5:95) as an eluent to give 80% (472 mg) of a colorless oil.

NMR ($CDCl_3$, 300 mHz)
1.8 - 1.3 (m, 10H, $(CH_2)_5$); 2.3 (S, 3H, CH_3-isoxazol) 2.7 (t, J=8Hz, 2H, -CH_2-isoxazol); 3.35 (t, J-8Hz, 2H, -CH_2-S); 3.9 (S, 9H, CH_3-N); 5.8 (S, 1H, H-isoxazol).
Analysis found: C, 52.65; H, 7.22; N, 23.78; S, 10.80
Required: $C_{13}H_{21}N_5OS$ = 295.403

C, 52.86; H, 7.17; N, 23.71; S, 10.85

Schematic f r Example 1

$$R-(CH_2)_n-Br + HS-R^1 \xrightarrow[\text{Acetone}]{K_2CO_3} R-(CH_2)_n-S-R^1$$

By procedures similar to those used in example 1 and starting with the appropriately substituted heterocyclic moiety R and R^1, the following compounds were prepared.

Example 2

5-[7-(5-methylthiodiazol-2-yl)thioheptyl]-3-methyl isoxazole. (2)
R = 3-methylisoxazol-5-yl
n = 7
R^1 = 5-methylthiodiazol-2-yl
Colorless prisms, mp 62 - 63° C, yield 55%
NMR ($CDCl_3$ 60 mHz).
1.3 - 2.00 (m, 10H, $(CH_2)_5$); 2.3 (S, 3H, CH_3-isoxazole); 2.7 (S, 3H, CH_3-thiodiazole); 2.7 (t, J=9Hz, 2H, -CH_2-isoxazole); 3.3 (t, J=9Hz, 2H, -CH_2-S), 5.8 (S, 1H, H-isoxazole) IR (neat).
Analysis found: C, 54.11; H, 6.89; N, 13.37; S, 20.52
Required: $C_{14}H_{21}N_3OS_2$ = 311.46
C, 53.99; H, 6.80; N, 13.49; S, 20.59

Example 3

5-[7-(1-methylimidazol-2-yl) thioheptyl]-3-methyl isoxazole. (3)
R = 3-methylisoxazol-5-yl
n = 7
R^1 = methylimidazol-2-yl
Yellow oil, yield 58%
NMR ($CDCl_3$, 200 mHz)
1.5 - 1.8 (m, 10H, $(CH_2)_5$), 2.3 (S, 3H, CH_3-isoxazole); 2.7 (t, J=8Hz, 2H, -CH_2-isoxazole); 3.05 (t, J=8Hz, 2H, -CH_2-S); 3.6 (S, 3H, CH_3-N); 5.8 (S, 1H, H-isoxazole); 6.85 (d, J=2Hz, 1H, H_5-imidazole); 7.05 (d, J=2Hz, 1H, H_4-imidazole).
Analysis found: C, 61.58; H, 7.17; N, 14.15; S, 10.81
Required: $C_{15}H_{23}N_3OS$ = 293.427
C, 61.40; H, 7.9; N, 14.32; S, 10.93

Example 4

5-[7-(benzimidazol-2-yl) thioheptyl]-3-methylisoxazole (4)
R = 3-methylisoxazol-5-yl
n = 7
R^1 = benzimidazol-2-yl
Colorless prisms, mp = 84 - 85°C, yield 72%
NMR ($CDCl_3$, 200 mHz)
1.3 - 1.75 (m, 10H, $(CH_2)_5$); 2.3 (S, 3H, CH_3-isoxazole); 2.7 (t, J=8Hz, 2H, -CH_2-isoxaz le); 3.3 (t, J=8Hz, 2H, -CH_2-S); 5.8 (S, 1H, H-isoxazole); 7.10 - 7.20 (m, 4H, H-benzimidazole); 7.50 (S, 1H, H-N).
Analysis found: C, 65.80; H, 7.11; N, 12.61; S, 9.65
Required: $C_{18}H_{23}N_3OS$
C, 65.62; H, 7.04; N, 12.75; S, 9.73

Example 5

5-[7-(5-chlorobenzimidazol-2-yl) thioheptyl]-3-methylisoxazole. (5)
R = 3-methylisoxazol-5-yl
n = 7
R^1 = 5-chlorobenzimidazol-2-yl
Sticky oil, yield 56%
NMR ($CDCl_3$, 200 mHz)
1.3 - 1.75 (m, 10H, $(CH_2)_5$); 2.3 (S, 3H, CH_3-isoxazole); 2.7 (t, J=8Hz, 2H, $-CH_2$-isoxazole); 3.3 (t, J=8Hz, 2H, $-CH_2$-S); 5.8 (S, 1H, H-isoxazole); 7.10 (d, J=2Hz, 1H, H_7-benzimidazole); 7.18 (d, J=2Hz, 1H-, H_6-benzimidazole); 7.25 (S, 1H, H_4-benzimidazole).
Analysis found: C, 59.55; H, 6.17; N, 11.42; S, 8.65, Cl, 9.63
Required: ($C_{18}H_{22}ClN_3OS$) = 363.905
C, 59.41; H, 6.09; N, 11.55; S, 8.81; Cl, 9.74

Example 6

5-[7-(benzothiazol-2-yl) thioheptyl]-3-methylisoxazole (6)
R = 3-methylisoxazol-5-yl
n = 7
R^1 = benzothiazol-2-yl
Colorless prism, mp = 50 - 57°C, yield 70%
NMR ($CDCl_3$, 200 mHz)
1.3 - 1.8 (m, 10H, $-(CH_2)_5-$); 2.3 (S, 3H, CH_3-isoxazole); 2.7 (t, J=8Hz, 2H, $-CH_2$-isoxazole); 3.3 (t, J=8Hz, 2H, $-CH_2$-S); 5.8 (S, 1H, H-isoxazole); 7.24 - 7.88 (m, 4H, H-benzothiazole).
Analysis found: C, 62.51; H, 6.51; N, 8.01; S, 18.39
Required: ($C_{18}H_{22}N_2OS_2$)
C, 62.39; H, 6.40; N, 8.08; S, 18.50

Example 7

1-[6-(5-methylthiodiazol-2-yl) thiohexyl]-3,5-dimethylpyrazole. (7)
R = 3,5-dimethylpyrazol-1-yl
n = 6
R^1 = 5-methylthiodiazol-2-yl
Colorless prism, mp = 40 - 42°C, yield 72%
NMR ($CDCl_3$)
1.3 - 1.9 (m, 8H, $-(CH_2)_4-$); 2.2 (S, 6H, Me_3-; Me_5-pyrazole); 2.7 (S, 3H, CH_3-thiodiazole); 3.3 (t, J=8Hz, 2H, CH_2-S); 3.95 (t, J=8Hz, 2H, $-CH_2$-N); 5.75 (S, 1H, H-pyrazole)
Analysis found: C, 54.31; H, 7.22; N, 17.93; S, 20.53
Required: ($C_{14}H_{22}N_4S_2$)
C, 54.16; H, 7.14; N, 18.05; S, 20.65

Example 8

1-[6-(1-methyltetrazol-5-yl) thiohexyl]-3,5-dimethylpyrazole. (8)
R = 3,5-dimethylpyrazol-1-yl
n = 6
R^1 = 1-methyltetrazol-5-yl
Yellow oil, yield 79%
NMR ($CDCl_3$)
1.3 - 1.9 (m, 8H, $-(CH_2)_4-$); 2.2 (S, 6H, Me_3-, Me_5-pyrazole); 3.3 (t, J=8Hz, 2H, $-CH_2$-S); 3.9 (S, 3H, CH_3-N of tetrazole); 3.95 (t, J=8Hz, 2H, $-CH_2$-N); 5.75 (S, 1H, H-pyrazole).
Analysis found: C, 53.19; H, 7.61; N, 28.42; S, 10.77
Required: ($C_{13}H_{22}N_6S$)
C, 53.04; H, 7.53; N, 28.53; S, 10.89

Example 9

1-[6-(1-methylimidazol-2-yl) thiohexyl]-3,5-dimethylpyrazole. (9)
R = 3,5-dimethylpyrazol-1-yl
n = 6
R^1 = 1-methylimidazol-2-yl
Colorless oil, yield 63%
NMR ($CDCl_3$)
1.3 - 1.9 (m, 8H, -$(CH_2)_4$-); 2.2 (S, 6H, Me_3-, Me_5-pyrazole); 3.05 (t, J=8Hz, 2H, CH_2-S); 3.6 (S, 3H, CH_3-N of imidazole); 3.95 (t, J=8Hz, 2H, -CH_2-N); 5.75 (S, 1H, H-pyrazole); 6.85 (d, J-2Hz, 1H, H_5-imidazole); 7.05 (d, J=2Hz, 1H, H_4-imidazole).
Analysis found: C, 61.83; H, 8.33; N, 18.99; S, 10.85
Required: ($C_{15}H_{24}N_4S$)
C, 61.61; H, 8.27; N, 19.16; S, 10.96

Example 10

1-[6-(benzoxazol-2-yl) thiohexyl]-3,5-dimethylpyrazole (10)
R = 3,5-dimethylpyrazol-1-yl
n = 6
R^1 = benzoxazol-2-yl
Yellow oil, yield 68%
NMR ($CDCl_3$)
1.3 - 1.9 (m, 8H, -$(CH_2)_4$-); 2.2 (S, 6H, Me_3-, Me_5-pyrazole); 3.3 (t, J=8Hz, 2H, CH_2-S); 3.95 (t, J=8Hz, 2H,-CH_2-N); 5.75 (S, 1H, H-pyrazole); 7.15 - 7.75 (m, 4H, H-benzoxazole)
Analysis found: C, 65.83; H, 7.12; N, 12.62; S, 9.61
Required: ($C_{18}H_{23}N_3OS$)
C, 65.62; H, 7.04; N, 12.75; S, 9.73

Example 11

2-[7-(benzoxazol-2-yl) thioheptyl]-4-methylthiazole (11)
R = 4-methylthiazole-2-yl
n = 7
R^1 = benzoxazol-2-yl
Yellow oil, yield 80%
NMR ($CDCl_3$)
1.4 - 1.9 (m, 10H, -$(CH_2)_5$-); 2.45 (S, 3H, CH_3-thiazole); 3.00 (t, J=8Hz, 2H, -CH_2-thiazole); 3.3 (t, J=8Hz, 2H, -CH_2-S); 6.75 (S, 1H, H-thiazole); 7.25 - 7.65 (m, 4H, H-benzoxazole).
Analysis found: C, 62.57; H, 6.51; N, 7.94; S, 18.32
Required: ($C_{18}H_{22}N_2OS_2$)
C, 62.39; H, 6.40; N, 8.08; S, 18.50

Example 12

2-[7-(5-chlorobenzimidazol-2-yl) thioheptyl]-4-methyl thiazole. (12)
R = 4-methylthiazol-2-yl
n = 7
R^1 = 5-chlorobenzimidazol-2-yl
Colorless prisms, mp = 110 - 112°C, yield 85%
NMR ($CDCl_3$)
1.3 - 1.9 (m, 10H, -$(CH_2)_5$-), 2.45 (S, 3H, CH_3-thiazol); 3.00 (t, J=8Hz, 2H, -CH_2-thiazole; 3.30 (t, J=8Hz, 2H, -CH_2-S); 6.75 (S, 1H, H-thiazole); 7.10 (d, J=2Hz, H_7-benzimidazole); 7.18 (d, J=2Hz, 1H, H_6-benzimidazole); 7.25 (S, 1H, H_4-benzimidazole).
Analysis found: C, 57.12; H, 5.91; N, 10.93; S, 16.76
Required: ($C_{18}H_{22}ClN_3S_2$)

C, 56.90; H, 5.84; N, 11.06; S, 16.88

Example 13

2-[6-(5-chlorobenzimidazole-2-yl) thioh xyl]-4-methylthiazol . (13)
R = 4-methylthiazol-2-yl
n = 6
R^1 = 5-chlorobenzimidazol-2-yl
Pale yellow prims, mp = 106 - 107°C, yield 64%
NMR ($CDCl_3$)
1.30 - 1.8 (m, 8H, -$(CH_2)4$-), 2.45 (S, 3H, CH_3-thiazole); 3.00 (t, J=8Hz, 2H, -CH_2-thiazole); 3.30 (t, J=8Hz, 2H, -CH_2-S); 6.75 (S, 1H, H-thiazole); 7.10 (d, J=2Hz, H_7-benzimidazole); 7.18 (d, J=2Hz, 1H, H_6-benzimidazole); 7.25 (S, 1H, H_4-benzimidazole).
Analysis found: C, 55.99; H, 5.58; N, 11.37; S, 17.42
Cl, 9.64
Required: ($C_{17}H_{20}ClN_3S_2$)
C, 55.80; H, 5.51; N, 11.48; S, 17.52; Cl, 9.69

Example 14

5-[6-(5-chlorobenzimidazol-2-yl) thiohexyl]-4-methylisothiazole. (14)
R = 4-methylisothiazol-5-yl
n = 6
R^1 = 5-chlorobenzimidazol-2-yl
Colorless prism, mp = 129 - 130°C, yield 72%
NMR ($CDCl_3$)
1.3 - 1.8 (m, 8H, -$(CH_2)_4$-); 2.15 (S, 3H, CH_3-isothiazole); 2.80 (t, J=8Hz, 2H, -CH_2-isothiazole); 3.30 (t, J=8Hz, 2H, -CH_2-S); 7.10 (d, J=2Hz, 1H, H_7-benzimidazole); 7.18 (d, J=2Hz, 1H, H_6-benzimidazole); 7.25 (S, 1H, H_4-benzimidazole); 8.15 (S, 1H, H-isothiazole); 9.25 (broad S, 1H, H-N)
Analysis found: C, 56.03; H, 5.60; N, 11.39; S, 17.37
Required: ($C_{17}H_{20}ClN_3S_2$)
C, 55.80; H, 5.51; N, 11.48; S, 17.52

Example 15

5-[6-(5-chlorobenzimidazol-2-yl) thiohexyl]isothiazole (15)
R = isothiazol-5-yl
n = 6
R^1 = 5-chlorobenzimidazol-2-yl
Colorless prism, mp = 86 - 87°C, yield 56%
NMR ($CDCl_3$)
1.3 - 1.8 (m, 8H, -$(CH_2)_4$-); 2.80 (t, J= 8Hz, 2H,-CH_2-isothiazole); 3.30 (t, J=8Hz, 2H, -CH_2-S); 6.95 (d, J=2Hz, 1H, H_4-isothiazole); 7.10 (d, J=2Hz, 1H, H_7-benzimidazole); 7.18 (d, J=2Hz, 1H, H_6-benzimidazole); 7.25 (S, 1H, H_4-benzimidazole); 8.35 (d, J=2Hz, 1H, H_3-isothiazole).
Analysis found: C, 54.83; H, 5.23; N, 11.85; S, 18.11
Required: ($C_{16}H_{18}ClN_3S_2$)
C, 54.61; H, 5.16; N, 11.94; S, 18.22

Example 16

1-[6-(1-methylimidazol-2-yl)sulfoxyhexyl]-3,5-dimethylpyrazole. (16)
R = 3,5-dimethylpyrazol-1-yl
n = 6
R^1 = methylimidazol-2-yl

1-[6-(1-methylimidazol-2-yl)mercaptohexyl]-3,5-dimethylpyrazole (1.63, 0.0055 mol) was dissolved in 50 ml of dichloromethane and cooled to 0°C. A portion of metachloroperbenzoic acid 80% (1.20 g, 0.0055 mol) was added to the solution while stirring. The mixture was brought to room temperature and stirred for 1/2 hour, 0.5

g of sodium bisulfite was added to destroy MCPBA excess. The mixture was washed with 5% aqueous solution of sodium bicarbonat (50 ml), and wat r (50 ml x 2). The organic layer was dried over sodium sulfate. Removal of the solvent gave a yellow il product which was purified by luti n from silica gel column using methanol-dichloromethane (5:95) as an eluant to gain 0.93 g light yellow il. Yield 55%

NMR ($CDCl_3$)

1.3 - 1.8 (m, 8H, -$(CH_2)_6$-); 2.2 (S, 6H, $2CH_3$-pyrazole); 3.45 (t, J=9Hz, 2H, CH_2-SO), 3.95 (t, J=8Hz, 2H, CH_2-N); 4.00 (S, 3H, CH_3-N); 5.75 (S, 1H, H-pyrazole); 7.1 (d, J=2Hz, 1H, H_5-imidazole); 7.2 (d, J=2Hz, 1H, H_4-imidazole) . IR (neat); 1076 cm^{-1}; (S=O)

Analysis found: C, 58.63; H, 7.95; N, 17.98; S, 10.21

Required: ($C_{15}H_{24}N_4OS$)

C, 58.41; H, 7.84; N, 18.16; S, 10.39

Schematic for Preparation of Sulfoxide Compounds

$$R-(CH_2)_m-S-R^1 \xrightarrow[CH_2Cl_2,\ RT]{MCPBA} R-(CH_2)_m-\overset{\overset{O}{\|}}{S}-R^1$$

By procedures similar to those used in Example 16, the following compounds were prepared.

Example 17

1-[6-(benzoxazol-2-yl) sulfoxyhexyl]-3,5-dimethylpyrazole. (17)

R = 3,5-dimethylpyrazol-1-yl

n = 6

R^1 = benzoxazol-2-yl

Yellow oil, yield 40%

1.3 - 1.9 (m, 8H, -$(CH_2)_4$-); 2.2 (S, 6H, Me_3-, Me_5-pyrazole); 3.45 (t, J=9Hz, 2H, CH_2-S=O); 3.95 (t, J=8Hz, 2H, -CH_2-N); 5.75 (S, 1H, H-pyrazole); 7.5 - 8.0 (m, 4H, H-benzoxazole). IR (neat); 1070 cm^{-1}; (S=O)

Analysis found: C, 62.81; H, 6.79; N, 12.07; S, 9.21

Required: ($C_{18}H_{23}N_3O_2S$)

C, 62.58; H, 6.71; N, 12.16; S, 9.28

Example 18

1-[6-(5-methylthiodiazol-2-yl) sulfoxyhexyl]-3,5-dimethylpyrazole. (18)

R = 3,5-dimethylpyrazol-1-yl

n = 6

R^1 = 5-methylthiodiazol-2-yl

Yellow oil, yield 24%

NMR ($CDCl_3$)

1.5 - 1.9 (m, 8H, -$(CH_2)_4$-); 2.2 (S, 6H, 2Me, Me_3-, Me_5-pyrazole); 2.9 (S, 3H, CH_3-thiodiazole); 3.45 (t, J=9Hz, -CH_2-S=O); 3.95 (t, J=8Hz, -CH_2-N); 5.75 (S, 1H, H-pyrazole). IR (neat); 1076 cm^{-1}; (S=O).

Analysis found: C, 51.72; H, 6.87; N, 17.01; S, 19.43

Required: ($C_{14}H_{22}N_4OS_2$)

C, 51.51; H, 6.79; N, 17.16; S, 19.64

Example 19

1-[6-(1-methyltetrazol-5-yl) sulfoxyhexyl]-2,5-dimethylpyrazole. (19)

R = 3,5-dimethylpyrazol-1-yl

n = 6

R^1 = 1-methyltetrazol-5-yl

Y llow oil, yield 20%
NMR ($CDCl_3$)
1.5 - 1.9 (m, 8H, -$(CH_2)_4$-); 2.2 (S, 6H, Me_3-, Me_5-pyrazole); 3.45 (t, J=9Hz, 2H, -CH_2-SO); 3.95 (t, J=8Hz, 2H, -CH_2-N); 4.35 (s, 3H, CH_3-N of t traz le); 5.75 (S, 1H, H-pyrazole). IR (neat); 1078 cm^{-1}; (S=O)
Analysis found: C, 50.54; H, 7.25; N, 26.85; S, 10.18
Required: ($C_{13}H_{22}N_6OS$)
C, 50.31; H, 7.14; N, 27.06; S, 10.33

Example 20

5-[7-(1-methyltetrazol-5-yl) sulfoxyheptyl]-3-methylisoxazole. (20)
R = 3-methylisoxazol-5-yl;
n = 7
R^1 = 1-methyltetrazol-5-yl
Yellow oil, yield 40%
NMR ($CDCl_3$)
1.5 - 1.8 (m, 10H, -$(CH_2)_5$-); 2.3 (S, 3H, CH_3-isoxazole); 2.70 (t, J=8Hz, 2H, -CH_2-isoxazole); 3.45 (t, J=9Hz, 2H, -CH_2=SO); 4.35 (S, 3H, CH_3-N of tetrazole); 5.8 (S, 1H, H-isoxazole). IR (neat); 1076 cm^{-1}; (S=O).
Analysis found: C, 50.33; H, 6.91; N, 22.35; S, 10.18
Required: ($C_{13}H_{21}N_5O_2S$)
C, 50.14; H, 6.80; N, 22.49; S, 10.30

Example 21

5-[7-(5-methylthiodiazol-2-yl) sulfoxyheptyl]-3-methylisoxazole. (21)
R = 3-methylisoxazol-5-yl;
n = 7
R^1 = 5-methylthiodiazol-2-yl
Colorless prism, mp = 80 - 82°C; yield 40%
NMR ($CDCl_3$)
1.5 - 1.8 (m, 10H, -$(CH_2)_5$-); 2.3 (S, 3H, CH_3-isoxazole); 2.70 (t, J=8Hz, 2H, -CH_2-isoxazole); 2.9 (S, 3H, CH_3-thiodiazole); 3.45 (t, J=9Hz, 2H, -CH_2-SO); 5.8 (S, 1H, H-isoxazole). IR (neat); 1078 cm^{-1}; (S=O)
Analysis found: C, 51.52; H, 6.54; N, 12.68; S, 19.43
Required: ($C_{14}H_{21}N_3O_2S_2$)
C, 51.35; H, 6.46; N, 12.83; S, 19.58

Example 22

5-[7-(1-methylimidazol-2-yl) sulfoxyheptyl]-3-methylisoxazole. (22)
R = 3-methylisoxazol-5-yl
n = 7
R^1 = 1-methylimidazol-2-yl
Yellow oil, yield 40%
NMR ($CDCl_3$)
1.5 - 1.8 (m, 10H, -$(CH_2)_5$-); 2.3 (S, 3H, CH_3-isoxazole); 2.70 (t, J=8Hz, 2H, -CH_2-isoxazole); 3.45 (t, J=9Hz, 2H, -CH_2-SO); 4.00 (S, 3H, CH_3-N); 5.8 (S, 1H, H-isoxazole); 7.05 (d, J=2Hz, 1H, H_5-imidazole); 7.15 (d, J=2Hz, 1H, H_4-imidazole). IR (neat); 1078 cm^{-1}; (S=O).
Analysis found: C, 58.44; H, 7.56; N, 13.45; S, 10.24
Reqired: ($C_{15}H_{23}N_3O_2S$)
C, 58.23; H, 7.49; N, 13.58; S, 10.36

Example 23

5-[7-(benzimidazol-2-yl) sulfoxyheptyl]-3-methylisoxazole. (23)
R = 3-methylisoxazol-5-yl
n = 7
R^1 = benzimidazol-2-yl

Col rless prism, mp = 56 - 58°C, yield 23%
NMR ($CDCl_3$)
1.3 - 1.9 (m, 10H, -$(CH_2)_5$-); 2.3 (S, 1H, H-isoxazole); 2.70 (t, J = 8Hz, 2H, -CH_2-isoxazole); 3.45 (t, J = 9Hz, 2H, -CH_2-SO); 5.8 (S, 1H, H-isoxazole); 7.3 - 7.5 (m, 4H, H-benzimidazole); 7.75 (broad S, 1H, H-N). IR (neat); 1076 cm^{-1}; (S=O)
Analysis found: C, 62.79; H, 6.79; N, 12.01; S, 9.15
Required: ($C_{18}H_{23}N_3O_2S$)
C, 62.58; H, 6.71; N, 12.16; S, 9.28

Example 24

2-[7-(benzoxazol-2-yl) sulfoxyheptyl]-4-methylthiazole. (24)
R = 4-methylthiazol-2-yl;
n = 7
R^1 = benzoxazol-2-yl
Yellow oil, yield 63%
NMR ($CDCl_3$)
1.4 - 1.9 (m, 10H, -$(CH_2)_5$-); 2.45 (S, 3H, CH_3-thiazole); 3.00 (t, J = 8Hz, 2H, -CH_2-thiazole); 3.45 (t, J = 9Hz, 2H, -CH_2-SO); 6.75 (S, 1H, H-thiazole); 7.45 - 7.9 (m, 4H, H-benzoxazole). IR (neat); 1065 cm^{-1}; (S=O)
Analysis found: C, 59.86; H, 6.21; N, 7.47; S, 17.48
Required: ($C_{18}H_{22}N_2O_2S_2$)
C, 59.64; H, 6.12; N, 7.73; S, 17.69

Example 25

5-[7-(1-methyltetrazol-5-yl) sulfoxyheptyl]-3-methylisoxazole. (25)
R = 3-methylisoxazol-5-yl;
n = 7
R^1 = methyltetrazol-5-yl

A mixture of 5-[7-(1-methyltetrazol-5-yl)mercaptoheptyl]-3-methylisoxazole (0.59 g, 0.002 mol) and metachloroperbenzoic acid 84% (0.817 g, 0.004 mol) in dichloromethane (40 ml) was stirred at room temperature for 3 hours. The mixture was washed with a solution of sodium hydroxide 2N (20 ml) and water (50 ml x 2). The organic layer was dried over sodium sulfate and evaporated to remove all the solvent to give a yellow solid product. The solid product was treated with hexane: ethyl acetate (4:1) (20 ml) and filtered. The remaining solid was recrystallized in hot ether to provide colourless prisms (350 mg). (yield 53%)
mp = 58 - 60°C
NMR ($CDCl_3$)
1.3 - 1.9 (m, 10H, -$(CH_2)_5$-); 2.3 (S, 1H, H-isoxazole); 2.70 (t, J = 8Hz, 2H, -CH_2-isoxazole); 3.45 (t, J = 9Hz, 2H, CH_2-SO_2); 4.3 (S, 3H, CH_3-N); 5.8 (S, 1H, 1H, H-isoxazole). IR (neat); 1145 cm^{-1}; (O=S=O)
Analysis found: C, 47.91; H, 6.58; N, 21.23; S, 9.68
Required: ($C_{13}H_{21}N_5O_3S$)
C, 47.69; H, 6.47; N, 21.39; S, 9.79

Example 26

2-[7-(benzoxazol-2-yl) sulfoxyheptyl]-4-methylthiazole. (26)
R = 4-methylthiazol-2-yl
n = 7
R^1 = benzoxazol-2-yl

2-[(benzoxazol-2-yl)mercaptoheptyl]-4-methylthiazole (1.362 g, 0.0039 mol) was dissolved in 25 ml of glacial acetic acid. After the addition of 5 ml of water, potassium permanganate (1.24 g, 0.0078 mol) was added to the solution while stirring at room temperature. The mixture was stirred for 30 minutes, the color of the solution changed from dark purple to brown, at which time 10 ml of hydrogen peroxide (30%) was added to decolorize the solution. 10 ml of ice + water was added to the mixture. The water and acetic acid were removed by evaporation under reduced pressur in a water bath. 1.5 g dark yellow oil, which was purified by elution from silica gel column using hexanes ethyl acetate (3:2) provided 0.586 g f a light yellow oil. yield 42%
NMR 1.4 - 1.9 (m, 10H, -$(CH_2)_5$-); 2.45 (S, 3H, CH_3-thiazole); 3.00 (t, J = 8Hz, 2H, -CH_2-thiazole); 3.45 (t, J = 9Hz, 2H, -CH_2-SO_2); 6.75 (S, 1H, H-thiazole); 7.50 - 8.05 (m, 4H, H-benzoxazole). IR (neat) 1162 cm^{-1}; (O=S=O)

Analysis found: C, 57.41; H, 5.94; N, 7.26; S, 16.72
Required: ($C_{18}H_{22}N_2O_3S_2$)
C, 57.12; H, 5.86; N, 7.40; S, 16.94

Schematic for Preparation of Sulfone Comp unds

$$R-(CH_2)_n-S-R^1 \xrightarrow[CH_2Cl_2]{MCPBA} R(CH_2)_n-\overset{\overset{O}{\|}}{\underset{\underset{O}{\|}}{S}}-R^1 \xleftarrow[CH_3COOH]{KMnO_4} R-(CH_2)_n-S-R^1$$

By the procedures similar to those used in example 25 and 26, the following compounds were prepared.

Example 27

5-[7-(5-methylthiodiazol-2-yl)sulfonylheptyl]-3-methylisoxazole. (27)
R = 3-methylisoxazol-5-yl
n = 7
R^1 = 5-methylthiodiazol-3-yl
Colorless prism, mp = 80 - 81°C, yield 45%
NMR ($CDCl_3$)
1.3 - 1.9 (m, 10H, -$(CH_2)_5$-); 2.3 (S, 1H, H-isoxazole); 2.70 (t, J=8Hz, 2H, CH_2-isoxazole); 2.9 (S, 3H, CH_3-thiodiazole); 3.45 (t, J=9Hz, 2H, -CH_2-SO_2); 5.8 (S, 1H, H-isoxazole). IR (neat); 1156 cm^{-1}; O=S=O.
Analysis found: C, 49.19; H, 6.25; N, 12.11; S, 18.51
Required: ($C_{14}H_{21}N_3O_3S_2$)
C, 48.96; H, 6.16; N, 12.23; S, 18.67

Example 28

1-[6-(5-methylthiodiazol-2-yl)sulfonylhexyl]-3,5-dimethylpyrazole. (28)
R = 3,5-dimethylpyrazol-1-yl
n = 6
R^1 = 5-methylthiodiazol-2-yl
Colorless prism, mp = 50 - 51°C, yield 23%
NMR ($CDCl_3$)
1.3 - 1.8 (m, 8H, -$(CH_2)_4$-); 2.2 (S, 6H, Me_3- Me_5-pyrazole); 2.9 (S, 3H, CH_3-thiodiazole); 3.45 (T, J=9Hz, 2H, CH_2-SO_2); 3.95 (t, J=8Hz, 2H, -CH_2-N); 5.75 (S, 1H, H-pyrazole). IR (neat); 1160 cm^{-1}; (O=S=O)
Analysis found: C, 49.33; H, 6.55; N, 16.19; S, 18.57
Required: ($C_{14}H_{22}N_4O_2S_2$)
C, 49.10; H, 6.47; N, 16.36; S, 18.72

Example 29

1-[6-(1-methyltetrazol-5-yl)sulfonylhexyl]-3,5-dimethylpyrazole. (29)
R = 3,5-dimethylpyrazol-1-yl
n = 6
R^1 = 1-methyltetrazol-5-yl
Yellow oil, yield 20%
NMR ($CDCl_3$)
1.3 - 1.9 (m, 8H, -$(CH_2)_4$-); 2.2 (S, 6H, Me_3-, Me_5-pyrazole); 3.45 (t, J=9Hz, 2H, CH_2-SO_2); 3.95 (t, J=8Hz, 2H, CH_2-N); 4.3 (S, 3H, CH_3-N); 5.75 (S, 1H, H-pyrazole). IR (neat); 1168 cm^{-1}; (O=S=O)
Analysis found: C, 48.06; H, 6.87; N, 25.55; S, 9.71
Reqired: ($C_{13}H_{22}N_6O_2S$)
C, 47.84; H, 6.79; N, 25.74; S, 9.82

Example 30

5-[7-(1-methylimidazol-2-yl)sulfonylheptyl]-3-methylisoxazole. (30)
R = 3-methylisoxazol-5-yl
n = 7
R^1 = methylimidazol-2-yl
Colorless prisms, mp = 54 - 55°C; yield 41%
NMR ($CDCl_3$)
1.5 - 1.8 (m, 10H, -$(CH_2)_5$-); 2.3 (S, 3H, CH_3-isoxazole); 2.70 (t, J=8Hz, 2H, -CH_2-SO_2); 4.00 (S, 3H, CH_3-N); 5.8 (S, 1H, H-isoxazole); 7.00 (3, J=2Hz, 1H, H_5-imidazole); 7.10 (d, J=2Hz, 1H, H_4-imidazole). IR (neat); 1160 cm^{-1}; (O=S=O)
Analysis found: C, 55.57; H, 7.21; N, 12.99; S, 9.61
Required: ($C_{15}H_{23}N_3O_3S$)
C, 55.36; H, 7.12; N, 12.91; S, 9.85

Anti-Rhinovirus Activity Experiments:

The experiments were performed by a cytopathic effect inhibition method and a neutral red dye uptake assay adapted from the method for activity against Herpes Simplex virus developed by M. Nixon Ellis, Ch. 18 Clinical Virology Manual - Specter, S. Lanoz, G. (1986).

Materials:

- WI38 cells (source ATCC)
- Rhinovirus Types: 1A, 1B, 2, 4, 15, 17, 23, 29, 30, 31, 32, 36, 39, 44, 49, 53, 56, 63, 86, 88 (source ATCC)
- Minimum Essential Medium, Eagle (Modified with Earles salt) supplemented with 10% Fatal bovine serum, 100 $iuml^{-1}$ penicillin G, 100μ gml^{-1} streptomycin and Non-Essential Aminoacids (Sigma M2025)
- Drugs dissolved in DMSO to 20 mg ml^{-1} and further diluted in the 10% FBS-MEM
- P.B.S. at pH 6.0
- Citrate/Methanol buffer (0.1M citric acid, 157.5 ml; 0.1 M Sodium Citrate, 92.5 ml; dionised H_2O 250 ml; methanol, 500 ml)
- Neutral red dye.

Procedure:

50 μl of each concentration of drug was added (in duplicate) to wells of a 96 well plate. Three wells per plate had medium instead of drug as cell or virus control. The wells were seeded with 100 μl of WI38 cells at 8.0×10^5 cells ml^{-1}. 50 μl of virus was added to each well at a dilution (usually 10 $TCID_{50}$) which would give 100% cytopathic effect after 3 days. A control plate was always set up in parallel which had no virus added. The plates were incubated at 33°C in a 95% air/5% CO_2, humidified atmosphere for 3-4 days. When 100% c.p.a. had developed (3-4 days) the cpa/toxic effect was first scored visually using an inverted microscope. The drug concentration at which virus growth was inhibited by 50% was called the minimum inhibitory concentration (MIC_{50}). The toxic concentration was calculated by noting the concentration at which there was a change in morphology in 25% of the cells compared to cell controls.

the plates were then subjected to the dye uptake assay. The plates were washed with phosphate buffered saline (P.B.S.) at pH 6.0. Then 250 μ l of 0.025% Neutral red/PBS pH 6.0 was added per well and incubated for 45 minutes at 37°C.

The plates were then washed again with PBS pH 6.0 and 250 μl of citrate-methanol buffer was added per well and incubated for 60 minutes at 37°C. The plates were then read on a multiscan spectrophotometer with a 540 mm filter. The cell control was denoted 100% and relative to this the concentration of drug inhibiting virus growth by 50% was termed MIC_{50}. If the concentration of the drug inhibited cell growth by 25% this was referred to as toxic.

It will be noted that the results obtained by the cytopathic effect inhibition method and the dye uptake method were usually identical, if not the higher value was quoted.

The selected compounds of this invention were tested against HRV-1A and HRV-39. The results are shown in Table I given herebelow.

Table I

T xicity and Activity (MIC-50) of Some Compounds (μ gml^{-1})

Compound No.	Toxicity	Rhinovirus-1A	Rhinovirus-39
WIN-51711 (Discxaril)	50	10	25
3	50	25	25
4	25	10	5
6	50	NA	10
10	50	NA	10
11	50	25	10
13	50	10	10
23	50	25	10
30	50	50	NA

MIC = Minimum Inhibitory Concentration

NA = Not Active

Compounds 4 and 13 which showed activity comparable to Disoxaril have been tested against twenty serotypes of Rhinoviruses (HRV's 1A, 1B, 2, 4, 15, 17, 23, 29, 30, 31, 32 36, 39, 44, 49, 53, 56, 63, 86, 88) to evaluate the range of activity in comparison therewith. The results are summarized in Table II, given below.

Table II

Toxicity and Activity (MIC50) of Soem Cmpounds (μ gml^{-1})

Compound No.	4	13	Disoxaril WIN-51711
Toxicity	25	50	50
Rhinovirus type			
1A	10	10	25
1B	NA	10	25
2	10	NA	NA
4	NA	5	0.5
15	5	5	5
17	5	5	< 0.5
23	5	5	10

2-[6-(5-chlorobenzimidazol-2-yl)thiohexyl)-4-methylthiazole (13) showed strog activity against coxsacki virus type 1B (MIC50 = 1 μ gml^{-1}. In comparison Disoxaril® had an MIC50 of 10 μ gml^{-1}.

In summary, the compounds of this invention can be utilized in the prevention or treatment of common cold, aspectic meningitis, myocarditis, and meningoencephalitis caused by rhinoviruses and coxsacki virus type B1.

The readers attention is directed to all papers and documents which are filed concurrently with this specification, and which are open to public inspection with this specification and the contents of all such papers and documents are incorporated herein by reference.

All of the features disclosed in this specification (including any accompanying claims, abstract and drawings), and/or all of the steps of any method or process so disclosed, may be combined in any combination, except combinations where at least some of such features and/or steps are mutually exclusive.

Each feature disclosed in the specification (including any accompanying claims, abstract and drawings), may be replaced by alternative features serving the same, equivalent or similar purpose, unless expressly stated otherwise. Thus, unless expressly stated otherwise, each feature disclosed is one example only of a generic series of equivalent or similar features.

The invention is not restricted to the details of the foregoing embodiment(s). The invention extends to any novel one, or any novel combination, of the features disclosed in this specification (including any accompanying claims, abstract and drawings), or to any novel one, or any novel combination, of the steps of any method or process so disclosed.

Claims

1. Compounds having the general formulae

$$R-(CH_2)_n-S-R^1; \quad R-(CH_2)_n-\overset{\displaystyle O}{\overset{\|}{S}}-R^1; \quad \text{or } R-(CH_2)_n-\overset{\displaystyle O}{\overset{\|}{\underset{\underset{\displaystyle O}{\|}}{S}}}-R^1$$

I II III

wherein R is an optionally substituted non-fused azole moiety;
n is 5, 6, 7 or 8; and
R^1 is an optionally substituted fused or non-fused azole moiety.

2. Compounds as claimed in Claim 1, wherein R is an optionally substituted isoxazolyl, thiazolyl, pyrazolyl or isothiazolyl group, optional substituent(s) being C_{1-4} alkyl group(s); and R^1 is an optionally substituted tetrazolyl, thiadiazolyl, benzoxazolyl, imidazolyl, benzimidoxazolyl or benzothiazolyl group, optional substituent(s) being selected from C_{1-4} alkyl group(s) and halogen atom(s).

3. Compounds of formula I, as claimed in Claim 1 or Claim 2, wherein R is selected from the group comprising 3-methylisoxazol-5-yl; 3,5-dimethylpyrazol-1-yl; 4-methylthiazol-2-yl; 4-methylisothiazol-5-yl; or 5-isothiazolyl;
n is 6 or 7; and
R^1 is selected from the group comprising 1-methyltetrazol-5-yl; 5-methyl-1,3,4-thiadiazol-2-yl; 2-benxoxazolyl; 1-methylimidazol-2-yl; 2-benzimidazoyl; 5-chlorobenzimidazol-2-yl; 2-benzothiazolyl.

4. A compound of formula I, as named in any one of Examples 1 to 30.

5. A phamaceutical composition, comprising a compound of general formula I as defined in any of Claims 1 to 4, together with a pharmaceutically acceptable carrier.

6. A compound as claimed in any of Claims 1 to 4, or a composition as claimed in Claim 5, for use as an active therapeutic substance.

7. A compound or composition as claimed in Claim 6, for use as an antiviral agent.

8. A process for the preparation of a compound of formula I, as defined in any one of Claims 1 to 4, which process comprises reacting a compound of the general formula
$R-(CH_2)-X$ II
wherein X represents a halogen atom,
with a fused or non-fused mercapto azole, to produce an unoxidised compound of formula I; and, when an oxidised compound of formula I is required, subjecting the unoxidised compound to an oxidation step.

European Patent Office

EUROPEAN SEARCH REPORT

Application number

EP 89303025.4

DOCUMENTS CONSIDERED TO BE RELEVANT			
Category	Citation of document with indication, where appropriate, of relevant passages	Relevant to claim	CLASSIFICATION OF THE APPLICATION (Int. Cl.4)
X	EP - A1 - 0 179 619 (JCJ) * Claim 1 * --	1	C 07 D 413/12 C 07 D 417/12 C 07 D 403/12 A 61 K 31/42 A 61 K 31/425 A 61 K 31/415
X	EP - A2 - 0 254 590 (YAMANOUCHI) * Claim 1 * --	1	
D,A	DE - A1 - 2 834 322 (STERLING) * Claims 1,10 * --	1,5-7	
D,A	US - A - 4 451 476 (DIANA) * Abstract * --	1,5-7	
D,A	EP - A2 - 0 137 242 (STERLING) * Claims 1,6,10 * --	1,5-7	TECHNICAL FIELDS SEARCHED (Int. Cl.4)
A	EP - A2 - 0 207 453 (STERLING) * Claims 1,8 * --	1,5-7	C 07 D 413/00 C 07 D 417/00 C 07 D 403/00

The present search report has been drawn up for all claims

Place of search	Date of completion of the search	Examiner
VIENNA	14-06-1989	HAMMER

CATEGORY OF CITED DOCUMENTS

X : particularly relevant if taken alone
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A : technological background
O : non-written disclosure
P : intermediate document

T : theory or principle underlying the invention
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D : document cited in the application
L : document cited for other reasons

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European Patent Offic

EUROPEAN SEARCH REPORT

Application number

-2-

EP 89303025.4

DOCUMENTS CONSIDERED TO BE RELEVANT			
Category	Citation of document with indication, where appropriate, of relevant passages	Relevant to claim	CLASSIFICATION OF THE APPLICATION (Int. Cl.4)
A	CHEMICAL ABSTRACTS, vol. 107, no. 19, November 09, 1987, Columbus, Ohio, USA MORGAN et al. "Synthesis and crystal structures of thioether-strapped porphyrins" page 695, column 2, abstract-no. 175 757g & J. Org. Chem. 1987, 52(20), 4628-31 --	1	
A	CHEMICAL ABSTRACTS, vol. 102, no. 15, April 15, 1985, Columbus, Ohio, USA OSHIMA et al. "Syntheses and characterization of β-forming poly[S-(ω-N-carbazolylalkyl)-L-cysteines]" page 669, column 2, abstract-no. 132 447k & J. Polym. Sci., Polym. Chem. Ed. 1984, 22(11, pt. 1), 3135-47 ----	1	TECHNICAL FIELDS SEARCHED (Int. Cl.4)

The present search report has been drawn up for all claims

Place of search	Date of completion of the search	Examiner
VIENNA	14-06-1989	HAMMER

CATEGORY OF CITED DOCUMENTS

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T : theory or principle underlying the invention
E : earlier patent document, but published on, or after the filing date
D : document cited in the application
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